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Synthetic studies on thiostrepton family of peptide antibiotics: synthesis of the cyclic core portion containing the dehydropiperidine, dihydroquinoline, L-valine, and masked dehydroalanine segments

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Abstract—The cyclic core portion containing the dehydropiperidine, dihydroquinoline, L-valine, and masked dehydroalanine (i.e., β-phenylselenoalanine) segments of the thiostrepton family of peptide antibiotics was synthesized via the consecutive coupling of these four segments followed by cyclization at the amide bond between the dehydropiperidine and masked dehydroalanine segments.

In the preceding letter[1] we reported the synthesis of the dihydroquinoline segment **1** of the thiostrepton family of peptide antibiotics (e.g., thiostrepton, siomycins A and C, and thiopeptin A_{1b}, Fig. 1).[2] In addition, we have already reported the synthesis of the dehydropiperidine,[3] another dihydroquinoline,[4] and pentapeptide[5] segments.[6,7] In this letter, we report the synthesis of the siomycin cyclic core portion **2** containing the dehydropiperidine, dihydroquinoline **1**, L-valine, and masked dehydroalanine (i.e., β-phenyl- selenoalanine) segments. The β-phenylselenoalanine portions in **2** would be transformed into the dehydroalanine portions during the final step of the total synthesis by the oxidative *syn*-elimination of the phenylseleno groups.[8]

We anticipated that the cyclic core portion **2** or its dehydroalanine derivative could be obtained by cyclization of **3** which has several types of the masked dehydroalanine substructures (e.g., the L- and/or D-β-phenylselenoalanine substructures) or the two dehydroalanine substructure via an intramolecular epoxide-opening reaction (Fig. 2). However, all efforts under a variety of reaction conditions resulted in the decomposition of **3** or no reaction.

Therefore, we investigated the intermolecular epoxide-opening reaction between the model quinoline epoxide **4**[9] (racemate) and L-valine benzyl ester **5** in the presence of several types of Lewis acids as an epoxide activator. The relevant experimental data are shown in Table 1. By our reported procedure[4] using $LiClO_4$,[10] a 1:1 mixture of the coupling product **6** (40% isolated yield as a 1:1 diastereomeric mixture) and 8-hydroxyquinoline (**7**) were obtained (entry 1). Other Lewis acids such as $Ti(i\text{-}PrO)_4$,[11] $Zn(OTf)_2$,[10] $Cu(OTf)_2$,[12] and $CeCl_3 \cdot 7H_2O$[13] were not effective for this coupling (entries 2–5). In the case of $Yb(OTf)_3$, which had been used as a catalyst for the epoxide-opening with amines by Crotti and co-workers[14a] and Yamamoto and co-workers,[14b] the success depended on the solvent used. In CH_2Cl_2,[14] the reaction resulted in a decomposition (entry 6). In THF,[14b] compounds **4**, **6**, and **7** were obtained in a

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Keywords: Thiostrepton; Dehydropiperidine; Dihydroquinoline; Dehydroalanine; Ytterbium triflate.

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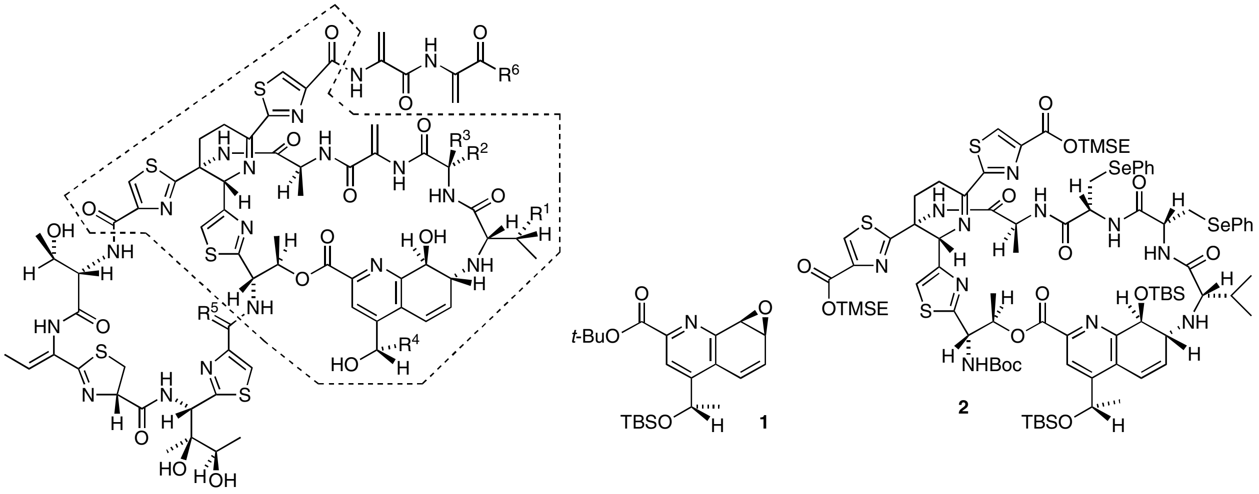
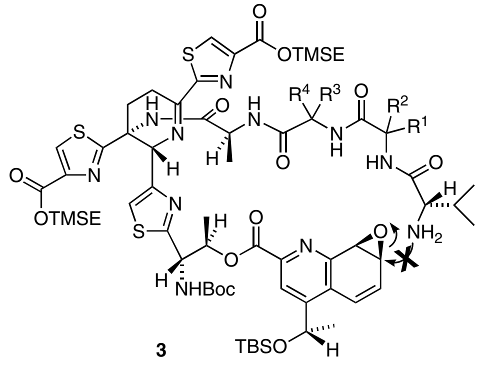


Thiostrepton: $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$
Siomycin A: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$
Siomycin C: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = OMe$
Siomycin D$_1$: $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = H$, $R^5 = O$, $R^6 = NH_2$
Thiopeptin A$_{1b}$: $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = S$, $R^6 = OMe$

Figure 1.



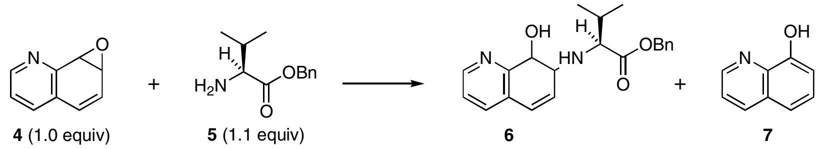
R^1, R^2 = H, CH_2SePh: R^3, R^4 = H, CH_2SePh
and
$R^1 = R^2 = CH_2$ (dehydroalanine): $R^3 = R^4 = CH_2$ (dehydroalanine)

Figure 2.

4:3:3 ratio (entry 7). The best result so far obtained was when a 1:10 CH_2Cl_2–H_2O was used as the biphasic solvent, affording **6** in 73% isolated yield together with an ca. 10% yield of the starting material **4** (entry 8). The presence of water seems to be crucial to this epoxide-opening reaction.[15]

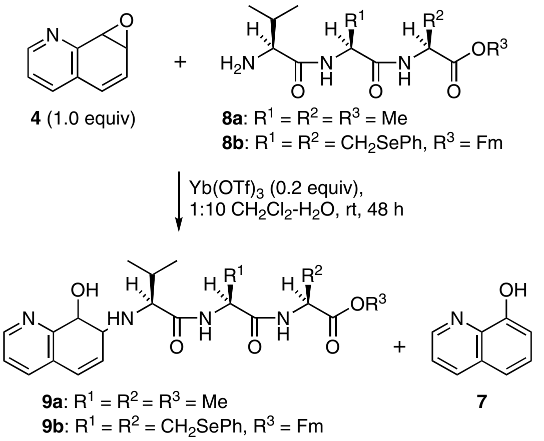
These results prompted us to investigate the reaction of **4** with tripeptide **8a**[16] (L-valine–L-alanine–L-alanine substructure) and **8b**[16] (L-valine–L-β-phenylselenoalanine–L-β-phenylselenoalanine substructure) (Scheme 1). Quinoline epoxide **4** (1.0 equiv) was treated with **8a** (1.1 equiv) in 1:10 CH_2Cl_2–H_2O in the presence of a catalytic amount (0.2 equiv) of $Yb(OTf)_3$ at rt for 48 h, giving a 15:76:9 mixture of **4**, **9a**, and **7**. In contrast, the coupling of **4** with **8b** under the same conditions afforded a 44:56 mixture of **4** and **7**; unfortunately, no **9b**

Table 1. Coupling reaction between **4** and **5**



Entry	Lewis acid (equiv)	Solvent	Temperature (°C)	Time (h)	Ratio[a] of **4**:**6**:**7**
1	$LiClO_4$ (5.0)	CH_3CN	70	15	0:49:51[b]
2	$Ti(i\text{-}PrO)_4$ (2.0)	THF	Reflux	25	90:10:0
3	$Zn(OTf)_2$ (1.0)	CH_3CN	rt	22	Decomposition
4	$Cu(OTf)_2$ (0.1)	CH_3CN	70	22	21:0:79
5	$CeCl_3{\cdot}7H_2O$ (0.5)	9:1 CH_3CN–H_2O	rt	22	No reaction
6	$Yb(OTf)_3$ (0.5)	CH_2Cl_2	rt	21	Decomposition
7	$Yb(OTf)_3$ (0.1)	THF	Reflux	30	40:30:30
8	$Yb(OTf)_3$ (0.2)	1:10 CH_2Cl_2–H_2O	rt	24	9:91:0[b]

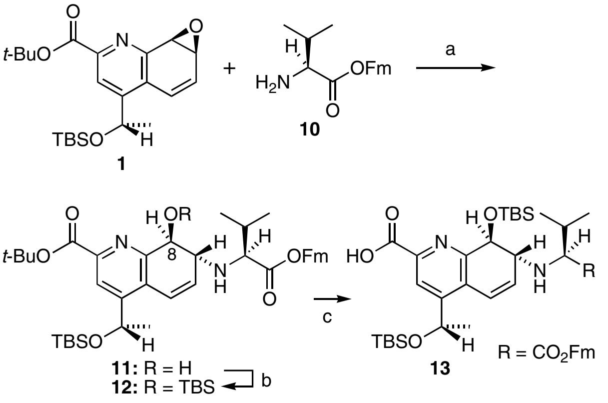
[a] The ratio of **4**:**6**:**7** was based on ^1H NMR analysis of the crude products.
[b] Isolated yield of **6** after silica gel column chromatography was 40% (entry 1) and 73% (entry 8).



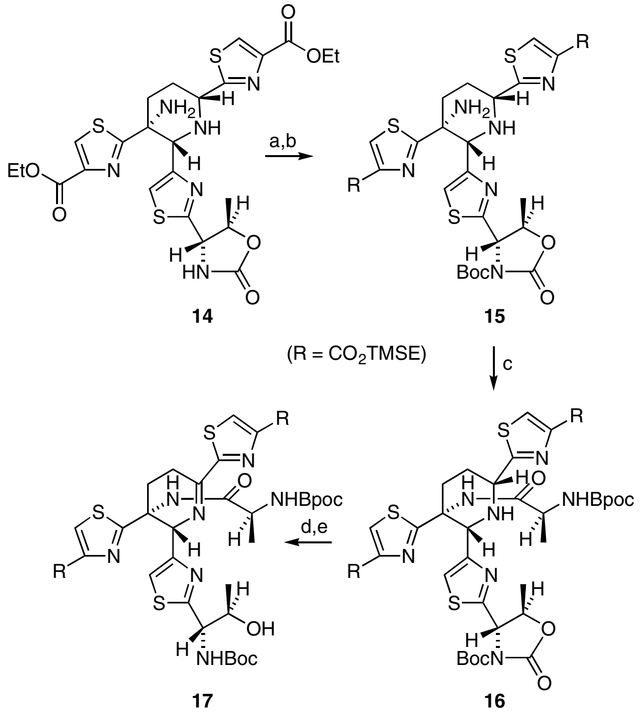
Scheme 1. Coupling reaction between **4** and **8**.

was obtained. Therefore, we selected the stepwise elongation of the L-valine and masked dehydroalanine (i.e., β-phenylselenoalanine) segments into the real dihydroquinoline segment **1**.

Along this line, dihydroquinoline **1**[1] (75% ee, 1.0 equiv) was coupled with L-valine 9-fluorenylmethyl (Fm) ester **10**[17] (2.0 equiv) in the presence of a catalytic amount (0.2 equiv) of $Yb(OTf)_3$ in 1:2 CH_2Cl_2–H_2O at rt to give **11** in 48% yield together with a 7% yield of the diastereomer of **11** arising from the enantiomer of **1**, a 6% yield of the regioisomer of **11**, and a 13% yield of the recovered **1** (Scheme 2). After silylation (96% yield) of **11**, the *t*-butyl ester of the resulting **12** was deprotected with *B*-bromocatecholborane[18] to give **13** in 79% yield.



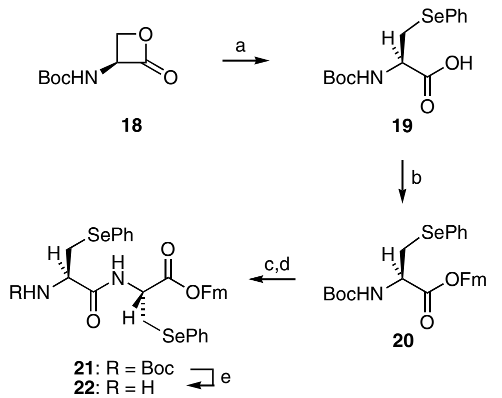
Scheme 2. Synthesis of dihydroquinoline carboxylic acid **13**. Reagents and conditions: (a) **1** (1.0 equiv), **10** (2.0 equiv), $Yb(OTf)_3$ (0.2 equiv), 1:2 CH_2Cl_2–H_2O, rt, 5 d, 48%; (b) TBSOTf (3.0 equiv), 2,6-lutidine (10 equiv), CH_2Cl_2, 0 °C, 15 min, 96%; (c) *B*-bromocatecholborane (2.0 equiv), CH_2Cl_2, rt, 1 d, 79%. Tf = trifluoromethanesulfonyl, TBS = *t*-butyldimethylsilyl.



Scheme 3. Synthesis of dehydropiperidine **17**. Reagents and conditions: (a) Ti(*i*-PrO)$_4$ (1.0 equiv), trimethylsilylethanol, 100 °C, 6 h; (b) Boc_2O (1.1 equiv), DMAP (0.2 equiv), Et_3N (1.1 equiv), THF, 0 °C, 1 h, 66%; (c) Bpoc-Ala-OH (2.0 equiv), CIP (2.0 equiv), HOAt (2.0 equiv), *i*-Pr_2NEt (5.0 equiv), CH_2Cl_2, rt, 1.5 h, 83%; (d) Cs_2CO_3 (1.0 equiv), trimethylsilylethanol, rt, 10 h; (e) *t*-BuOCl (1.1 equiv), THF, −78 °C, 1 h, then DMAP (0.2 equiv), Et_3N (10 equiv), rt, 3 h, 61%. TMSE = trimethylsilylethyl, Boc = *t*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, Bpoc = 1-methyl-1-(4-biphenylyl)ethoxycarbonyl, CIP = 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.

The coupling partner, the dehydropiperidine segment **17**, was prepared from **14** (Scheme 3), which was a synthetic intermediate of our former dehydropiperidine segment.[3] Since it seems apparent that the ethyl esters cannot be hydrolyzed after the construction of the cyclic peptide which contains the lactone function, these ethyl esters were changed to the trimethylsilylethyl (TMSE) protecting groups. The treatment of **14** with trimethylsilylethanol in the presence of Ti(*i*-PrO)$_4$[19] followed by the Boc protection of the oxazolidinone amine gave **15** in 66% yield. Condensation of **15** (1.0 equiv) with Bpoc-Ala-OH[20] (2.0 equiv) using CIP,[21] HOAt, and *i*-Pr_2NEt afforded **16** in 83% yield. The selective deprotection of the oxazolidinone in the presence of the TMSE esters was realized by Cs_2CO_3[22] in trimethylsilylethanol and the successive chlorination with *t*-BuOCl[23] and dehydrochlorination with triethylamine and DMAP gave the dehydropiperidine segment **17** in 61% yield.

The preparation of the β-phenylselenoalanine dipeptide **22**, the masked precursor to the labile dehydroalanine portion, started with the known Boc-L-serine β-lactone **18**[24] (Scheme 4). Phenylselenylation of **18** by the procedure reported by us[5] (PhSeH, DMF, rt, 2 h) gave **19**,[25] which was treated with 9-fluorenylmethanol,[26] and DCC in the presence of a catalytic amount of DMAP to give fluorenylmethyl (Fm) ester **20** in 82% yield from **18**. The acidic treatment of **20** followed by condensation with **19** using CIP, HOAt, and *i*-Pr_2NEt in CH_2Cl_2 afforded **21** in 88% yield. The treatment of **21** with TFA provided dipeptide **22**, which was used without purification for the next step.



Scheme 4. Synthesis of β-phenylselenoalanine dipeptide **22**. Reagents and conditions: (a) PhSeH (1.2 equiv), DMF, rt, 2 h; (b) 9-fluorenylmethanol (1.2 equiv), DCC (1.2 equiv), DMAP (0.2 equiv), CH_2Cl_2, rt, 4 h, 82% (two steps); (c) 1:1 TFA–CH_2Cl_2, rt, 1 h, aq $NaHCO_3$ work-up; (d) **19** (1.1 equv), CIP (1.1 equiv), HOAt (1.1 equiv), *i*-Pr_2NEt (2.5 equiv), CH_2Cl_2, rt, 1 h, 88% (two steps); (e) 1:1 TFA–CH_2Cl_2, rt, 0.5 h, aq $NaHCO_3$ work-up. DCC = 1,3-dicyclohexylcarbodiimide, TFA = trifluoroacetic acid.

With all the segments in hand, we next focused on their coupling and cyclization (Scheme 5). Condensation of dehydropiperidine **17** (1.2 equiv) and dihydroquinoline **13** (1.0 equiv) was realized with CIP, DMAP, and *i*-Pr_2NEt in CH_2Cl_2 to give **23** in 67% yield. After deprotection of the Fm ester in **23** with 1:1 diethylamine–CH_2Cl_2,[26] the resulting carboxylic acid (1.0 equiv) was coupled with the third segment **22** (1.2 equiv) with CIP, HOAt, and *i*-Pr_2NEt in CH_2Cl_2 to give **24** in 94% yield from **23**. Deprotection of the Bpoc group in **24** with $Mg(ClO_4)_2$[27] in acetonitrile followed by deprotection of the Fm group afforded the cyclization precursor **25** in 67% yield. Final cyclization was carried out under a variety of condensation conditions including EDC–HOAt–NMM, PyBOP–*i*-Pr_2NEt,[28] DPPA–*i*-Pr_2NEt,[29] and HATU–base.[30] Among them, the best conditions were HATU (5.0 equiv) and NMM (5.0 equiv) in CH_2Cl_2 (1 mM for **25**) at rt for 1 d, affording **2**[31] in 79% yield. The structure of **2** was confirmed by the mass spectrum and the ^1H and ^{13}C NMR spectra, including H–H COSY, HMQC, and HMBC.

In summary, we have synthesized the siomycin cyclic core portion **2** containing the dehydropiperidine, dihydroquinoline, L-valine, and masked dehydroalanine segments via the consecutive coupling of these four segments, followed by cyclization at the amide bond between the dehydropiperidine and masked dehydroalanine segments. Synthetic studies for the total synthesis of the thiostrepton family of peptide antibiotics are now in progress.

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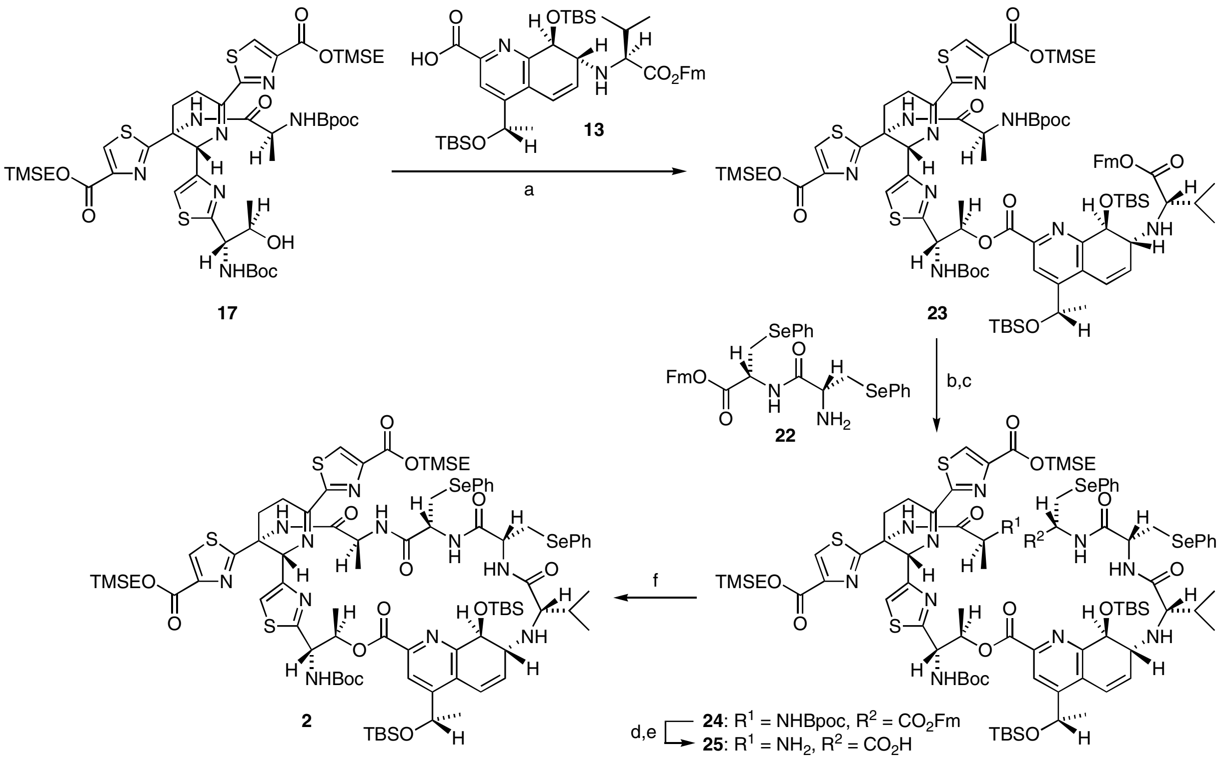

Scheme 5. Synthesis of the cyclic core portion **2**. Reagents and conditions: (a) **17** (1.2 equiv), **13** (1.0 equiv), CIP (1.2 equiv), DMAP (0.5 equiv), *i*-Pr_2NEt (2.5 equiv), CH_2Cl_2, rt, 10 min, 67%; (b) 1:1 Et_2NH–CH_2Cl_2, rt, 1 h; (c) **22** (1.2 equiv), CIP (1.2 equiv), HOAt (1.2 equiv), *i*-Pr_2NEt (2.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, 94% (two steps); (d) $Mg(ClO_4)_2$ (5.0 equiv), acetonitrile, 40 °C, 5.5 h; (e) 10% Et_2NH–CH_2Cl_2, rt, 2.5 h, 67% (two steps); (f) HATU (5.0 equiv), NMM (5.0 equiv), CH_2Cl_2 (1 mM for **25**), rt, 1 d, 79%. HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, NMM = *N*-methylmorpholine.

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31. Data of **2**: $[\alpha]_D^{27}$ −85.2 (*c* 1.00, CHCl$_3$); IR (KBr): 2955, 2895, 2860, 2360, 1720, 1500, 1480, 1405, 1255, 1220, 1095, 840, 780, 695 cm^{-1}; ^{1}H NMR (CD$_3$OD, 300 MHz, 40 °C) 8.28 (quinoline H-3, 1H, s), 8.26 (thiazole H-5, 1H, s), 7.94 (thiazole H-5, 1H, s), 7.53–7.40 (Ph, 4H, m), 7.30–7.12 (Ph, 6H, m), 7.27 (thiazole H-5, 1H, s), 6.89 (quinoline H-5, 1H, d, $J = 10.0$ Hz), 6.40 (quinoline H-6, 1H, dd, $J = 5.4$, 10.0 Hz), 5.85 (Thr-β, 1H, m), 5.52 (piperidine H-6, 1H, br s), 5.31 (MeC*H*(OTBS), 1H, q, $J = 6.2$ Hz), 5.21 (Thr-α, 1H, m), 4.94 (quinoline H-8, 1H, br s), 4.74–4.60 (2 × PhSeAla-α, 2H, m), 4.52–4.33 (2 × Me$_3$SiCH$_2$*CH*$_2$, 4H, m), 4.20 (Ala-α, 1H, q, $J = 7.0$ Hz), 3.52–2.68 (2 × PhSeAla-β, piperidine H-3 and H-4, Val-α, 9H, m), 3.38 (quinoline H-7, 1H, dd, $J = 1.2$, 5.4 Hz), 2.01 (Val-β, 1H, m), 1.40 (*Me*CH(OTBS), 3H, d, $J = 6.2$ Hz), 1.40 (Thr-γ, 3H, d, $J = 6.2$ Hz), 1.33 (Boc, 9H, s), 1.30 (Ala-β, 3H, d, $J = 7.0$ Hz), 1.20–1.04 (2 × Me$_3$Si*CH*$_2$CH$_2$, 4H, m), 0.98 (Val-γ, 3H, d, $J = 7.0$ Hz), 0.95 (*t-Bu*Me$_2$Si, 9H, s), 0.81 (Val-γ, 3H, d, $J = 6.8$ Hz), 0.69 (*t-Bu*Me$_2$Si, 9H, s), 0.10 and 0.08 (2 × *Me*$_3$SiCH$_2$CH$_2$, 18H, each s, contaminated with 6H of 2 × *t*-Bu*Me*$_2$Si), −0.01 (*t*-Bu*Me*$_2$Si, 3H, s), −0.30 (*t*-Bu*Me*$_2$Si, 3H, s); ^{13}C NMR (CD$_3$OD, 75 MHz, 40 °C) : δ 176.6, 176.3, 175.1, 172.4, 171.1, 170.8, 165.9, 164.5, 162.8, 156.9, 156.9, 153.8, 152.5, 149.0, 148.1, 146.6, 134.2, 133.9, 132.4, 132.0, 131.6, 130.3, 130.2, 128.9, 128.4, 128.2, 128.1, 123.7, 122.9, 121.0, 81.6, 74.0, 73.1, 68.5, 67.8, 67.7, 67.3, 64.7, 64.6, 61.5, 61.3, 55.0, 52.6, 32.8, 30.4, 28.9, 28.6, 28.2, 26.4, 26.2, 26.0, 19.8, 19.1, 18.9, 18.3, 18.2, 18.0, −1.4, −1.4, −4.0, −4.1, −4.6, −4.6; LRMS (MALDI-TOF) Calcd for C$_{84}$H$_{121}$N$_{11}$O$_{14}$S$_3$Se$_2$Si$_4$Na (M+Na)$^+$: 1898.6. Found: 1898.5.